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MANAGING PATIENTS WITH PAPILLARY THYROID CARCINOMA: INSIGHTS GAINED FROM THE MAYO CLINIC'S EXPERIENCE OF TREATING 2,512 CONSECUTIVE PATIENTS DURING 1940 THROUGH 2000

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ABSTRACT

2,512 consecutive patients with papillary thyroid carcinoma (PTC) were managed during 1940 through 2000 at the Mayo Clinic. During that period, there were two significant therapeutic trends. The first was a change in surgical practice during 1940–69 from an initial unilateral lobectomy (UL) to a bilateral lobar resection (BLR). The second was the increasing use since 1970 of I-131 for radioactive-iodine remnant ablation (RRA). The advent of BLR resulted in significantly improved tumor recurrence (TR) rates in both low-risk (MACIS scores < 6) and high-risk (MACIS scores 6+) patients, and also reduced cause-specific mortality (CSM) in high-risk patients. By contrast, RRA did not significantly improve the outcome (either CSM or TR) in low-risk (MACIS < 6) patients previously treated with initial near-total or total thyroidectomy. These data encourage a more selective use of I-131 in PTC management and do not lend support to the current widespread use of RRA in low-risk PTC.

INTRODUCTION

Papillary thyroid carcinoma (PTC) represents the commonest endocrine malignancy (1), and in recent American and Japanese surveys it has accounted for at least 80% of new cases of thyroid cancer (2,3). The management of PTC has been controversial (4) since at least 1959, and therapeutic issues have continued to be debated over the next four decades (5,6). One reason for a lack of consensus has been the dire lack of any long-term prospective controlled therapeutic trials (1,7). Conse-

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quently, all current treatment recommendations for PTC patients have been based almost entirely on results derived from multivariate analysis of relatively uncontrolled retrospective studies (8). This has not, however, prevented societies of endocrinologists (9,10), surgeons, (11,12) and oncologists (13) from producing in recent years very specific practice guidelines for the treatment of this increasingly recognized entity. The clear message from these recommendations is that in the 21st century most PTC patients in the United States will likely be considered eligible for an initial near-total or total thyroidectomy, almost routinely followed by "completion" of the thyroidectomy by postoperative administration of radioactive iodine (RAI) for remnant ablation (13,14,15). It is not at all clear whether such an aggressive approach is justifiable (1,6,7,16).

At the Mayo Clinic in Rochester, Minnesota, there has long been a tradition of analyzing the results of surgical treatment in thyroid cancer. Balfour (17) in 1918 reported on 63 operable patients treated during 1910–16, and 50 years later Woolner (18) described long-term follow-up information on 1,181 cases of thyroid cancer treated from 1926 to 1960. By 1986, McConahey (19), describing a cohort of 859 PTC patients managed at Mayo during 1946–70, found that the overall mortality observed at 30 years was only 3% above that expected. Such excellent outcome results were accomplished despite the fact that only 16% underwent total thyroidectomy, and 97% did not have radioiodine remnant ablation (RRA). More recent analyses of Mayo patients treated since 1970 have raised serious doubts about the efficacy of RRA (1,7), particularly in patients judged to be at low-risk (6,20) of either cause-specific mortality (CSM) or tumor recurrence (TR).

In terms of PTC management at Mayo Clinic, the period from 1940 through 2000 can be conveniently divided into four therapeutic eras (1,7). In the first (1940–54), most PTC patients got a unilateral lobectomy, few got near-total or total thyroidectomy, and almost none got RRA (4). In the second (1955–69), the majority had initial near-total thyroidectomy, and less than 5% were ablated (19). During 1970–84 most PTC patients had near-total thyroidectomy or total thyroidectomy, and about a third were ablated (7). Since 1985, almost all PTC patients had an initial near-total or total thyroidectomy, and almost 50% were ablated. What is unclear is whether the increased aggressiveness of PTC management, especially since 1975, has translated into improved outcome in terms of long-term CSM and TR rates. The present study was devised initially to clarify the changes in therapy for PTC patients occurring at Mayo during 1940 through 2000. However, even more importantly, the study was aimed at determining whether

the observed trend towards more aggressive therapy led to significantly improved outcome, especially for CSM and TR. Of particular interest was our intent to quantify the influence of RRA after adequate initial surgery on outcome in the majority (almost 85%) of PTC patients, who would be considered at extremely low-risk of developing threatening tumor recurrences or dying of thyroid malignancy.

MATERIALS AND METHODS

Patients and Follow-Up

The records of all patients treated at the Mayo Clinic, Rochester, Minnesota, for PTC during 1940 through 2000 were reviewed. All relevant histologic slides were re-examined and reclassified according to the 1988 World Health Organization criteria (21) by a Mayo staff endocrine pathologist, who had no knowledge of disease outcome. There were 2,512 patients (1,690 females: 822 males) who underwent definitive primary surgical therapy at the Mayo Clinic, had histologic re-confirmation of PTC, and were treated within 60 days of the initial diagnosis. Details of initial presentation, therapy, and outcome of these 2,512 patients, consecutively treated during 1940 through 2000, were recorded in a computerized database. Death certificates were examined for the 771 (31%) who were known to have died. Information regarding living patients was obtained by reexamination or by correspondence with the home physician, patient, or relatives (6,7,20). There were a total of 43,095 person-years of follow-up. Median follow-up was 14 years, and the longest follow-up was 60 years. Death was from PTC in 106 (4%). Excluded from the studies of tumor recurrence were those 142 (6%) who had either distant metastasis discovered within 30 days of the initial surgery or had incomplete tumor resection, with gross residual disease persisting after resection.

Statistics

Comparisons of risk characteristics and trends during the 61-year period studied were performed using Chi-square tests of proportions or Fisher's exact test where necessary. Survival from the date of initial surgery to each endpoint (including CSM and TR) was analyzed using the Kaplan-Meier method (22). The log-rank test was used to determine group differences in survival curves (23). All tests were 2-sided, with alpha level of 0.05. All calculations were performed using SAS software (24).

RESULTS

Patient and Tumor Characteristics

The median age of the patient at diagnosis of PTC was 46 years, with a range from 4 to 90 years. Mean tumor size was 2.1 cm (median 1.7 cm), with a range from 0.1 cm to 15 cm in maximum diameter. Tumor size was 1.5 cm or less in 1,207 (48%). Histologic grade (7,19) was 1, 2, and 3 in 2,395 (95%), 111, and 6, respectively. DNA ploidy by flow cytometry (7) was diploid in 78%, tetraploid in 11%, and aneuploid in 11% of 471 cases studied. Tumors were demonstrated to be multicentric in 715 (28%). 332 (13%) of primary tumors were at presentation locally invasive of extra-thyroidal soft tissues, 1,011 (40%) had metastatic involvement of regional lymph nodes at time of initial surgery, and 47 (2%) had distant metastases found no later than 30 days after the date of the initial surgical procedure. Figure 1 illustrates the distributions of pTNM stages (25) and presenting MACIS prognostic scores (26). There were 2,031 PTC patients (81%) who were either stage I or II at diagnosis, while 2,099 (84%) had MACIS scores of < 6 (low-risk). The median MACIS score was 4.43, and the range of scores was from 3.15 to 15.34 (mean score 4.80). During the four eras studied, the proportion of low-risk PTC patients, with initial MACIS scores < 6, were 78% in 1940–54, 84% in 1955–69, 86% in 1970–84, and 84% in 1985–2000.

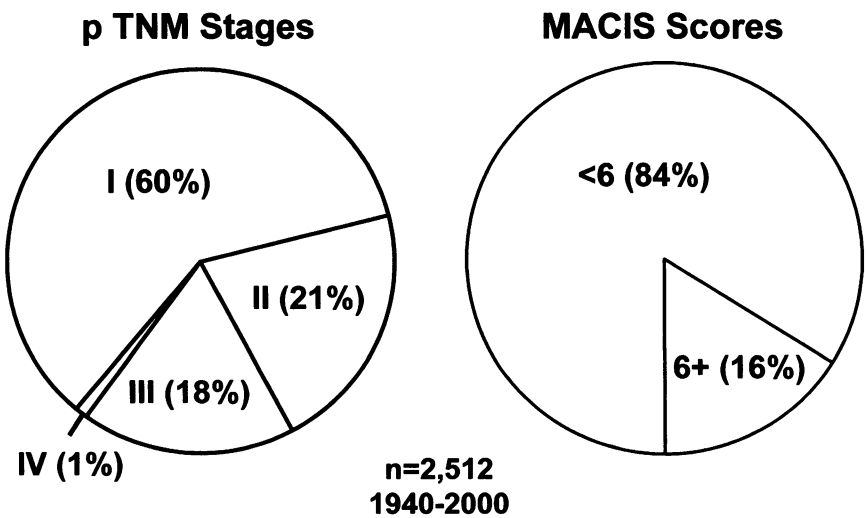

FIG. 1. Distributions of pTNM stages and MACIS scores in 2,512 consecutively treated PTC patients managed at the Mayo Clinic during 1940 through 2000.

Initial Surgery and Postoperative RAI Administration

Bilateral lobar resection, performed in 2,179 (87%), was the usual primary surgical procedure performed on PTC patients during the period of study. Overall, the most frequently performed primary surgical procedure was near-total thyroidectomy, which accounted for 1,324 (53%) of the initial operations. Total thyroidectomy was the second most popular operation during the 61 years studied, and was performed in 635 cases (25%). Bilateral subtotal resection was performed in only 220 (9%). Unilateral thyroid lobectomy was the primary surgical procedure in 293 (12%), while lesser procedures (including biopsy and subtotal lobectomy) were performed in the remaining 1% of patients. In only 108 (4%) of cases was there incomplete tumor excision, where the surgeon reported the persistence of gross residual disease at the conclusion of the initial neck operation. There were 2,370 patients (94%) who had complete surgical resection and no distant metastasis on initial examination or within 30 days of primary operation. These potentially curable patients were considered eligible for postoperative RAI adjunctive therapy. At least 797 (32%) were given such therapy up to many years after the primary operation, but only 662 (26%) had radioiodine remnant ablation (RRA) performed within 6 months of initial surgery.

Trends in Extent of Surgical Resection

Figure 2 illustrates the significant changes ($P < 0.0001$) that occurred in the extent of initial surgical resection performed at Mayo for the definitive therapy of PTC during the four eras studied. During the first 30 study years, the proportion having lobectomy fell from 52% during 1940–54 to only 5% during 1955–69. During the period of 1940 through 1954, 28% had either near-total or total thyroidectomy, but this figure rose to 86% during 1955–2000. Overall, the most significant differences occurred in the relative proportions of patients having either lobectomy or bilateral lobar resection (BLR). As illustrated by Figure 3 (left panel), these changes mainly occurred during the first 30 years of the study. During the 1940–54 period, only 43% underwent initial BLR, but this proportion rose to 94% during 1955–69, achieved a peak rate of 97% during 1970–84, and latterly was 91% during 1985–2000.

Trends in Remnant Ablation after BLR

Figure 3 (right panel) illustrates the increasing frequency of RRA performed during 1940 through 2000, and demonstrates the ten-fold increase between the second (1955–69) and third era (1970–84) stud-

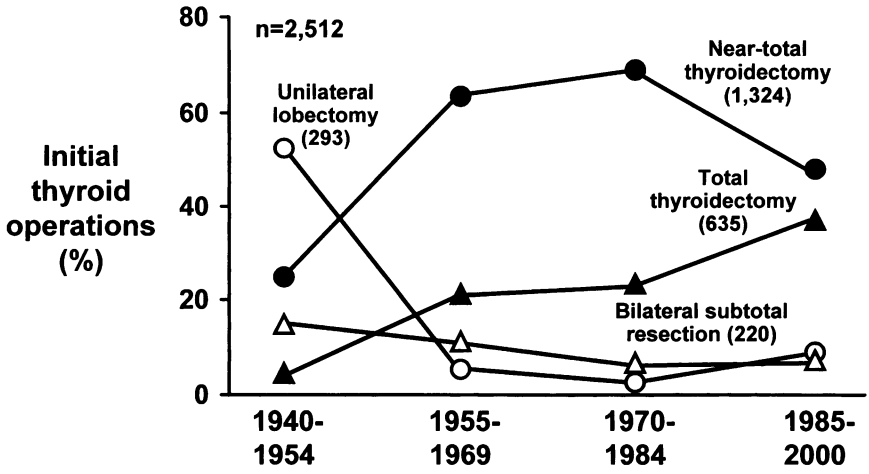

FIG. 2. Trends in the extent of initial surgical resection performed at the Mayo Clinic for the definitive therapy of PTC. Numbers in parentheses represent the numbers of patients having that specific type of initial surgery during 1940 through 2000.

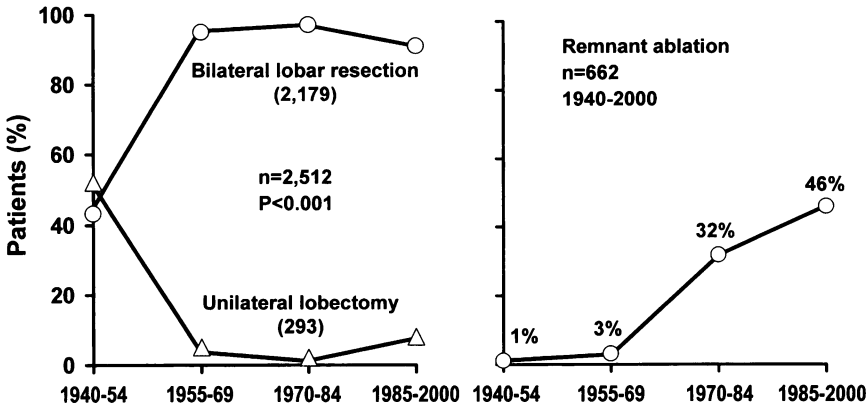

FIG. 3. Trends in the (left panel) extent of initial surgery, and (right panel) the proportion of patients having radioiodine remnant ablation (RRA) after initial bilateral lobar resection (BLR) at Mayo Clinic during 1940 through 2000.

ied. Only 2 PTC patients (1%) were treated with RRA at Mayo during 1940–54, and during 1955–69 only 20 (4%) of 523 patients, treated by initial BLR, were ablated. During 1970–84 and 1985–2000, the comparable proportions undergoing RRA were 34% and 51%, respectively. Figure 4 highlights the significant changes in use of RRA occurring in the 1,423 patients who had potentially curative BLR during 1970 through 2000 ($P < 0.001$). During 1970–74 only 6% of 149 patients

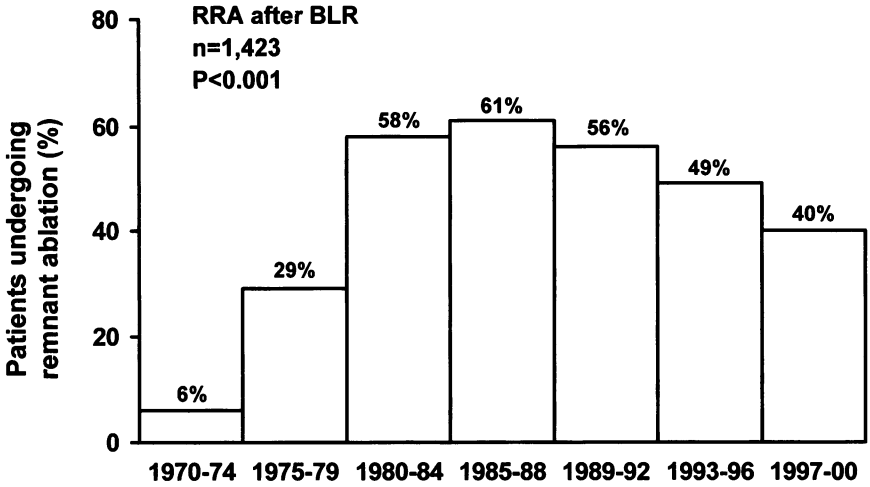

FIG. 4. Changing frequency of remnant ablation at Mayo Clinic during 1970 through 2000 in 1,423 patients, without initial distant metastases, who underwent RRA within 6 months of potentially curative bilateral resection (BLR).

underwent RRA, but this increased very dramatically to 29% of 205 patients treated during 1975–79. The highest RRA rate (of 61%) was found in the period of 1985–88. During 1993–96, this rate had fallen to 49%, and by 1997 through 2000, the comparable rate was further reduced to 40% of PTC patients undergoing BLR with complete surgical resection.

Overall Postoperative Outcome

To date, 106 (4%) have died directly from PTC, and 771 (31%) have died from all causes of mortality. For a comparable population living in the North Central United States during this period, the expected number of deaths from all causes would have been 700, an excess of 71 deaths that is highly significant ($P = 0.006$). If one considers the survival to death from all causes in the potentially surgically cured group of 2,370 (having complete surgical resection and presenting with disease localized to the neck), the observed number of deaths was 673, insignificantly different ($P = 0.963$), from the 672 expected.

Figure 5 illustrates the CSM and TR rates observed over 25 postoperative years in the total group of 2,512 patients. CSM rates were 5% at 15, 20, and 25 years. The TR rates were 8% at 5, and 10% at 10 postoperative years for the subgroup of 2,370, who had localized disease, which was completely excised at initial surgery. By 25 years the TR rate was 14%, and between 25 and 40 postoperative years this figure only rose by one more percent to 15%. Figure 6 demonstrates

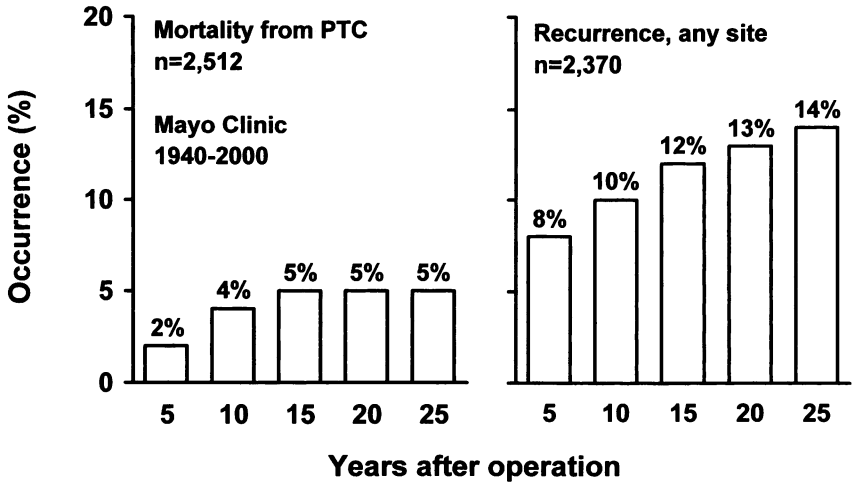

FIG. 5. Overall outcome of 2,512 consecutively treated PTC patients managed at Mayo Clinic during 1940 through 2000, demonstrating 5- to 25-year rates for (left panel) cause-specific mortality and (right panel) tumor recurrence at any anatomic site.

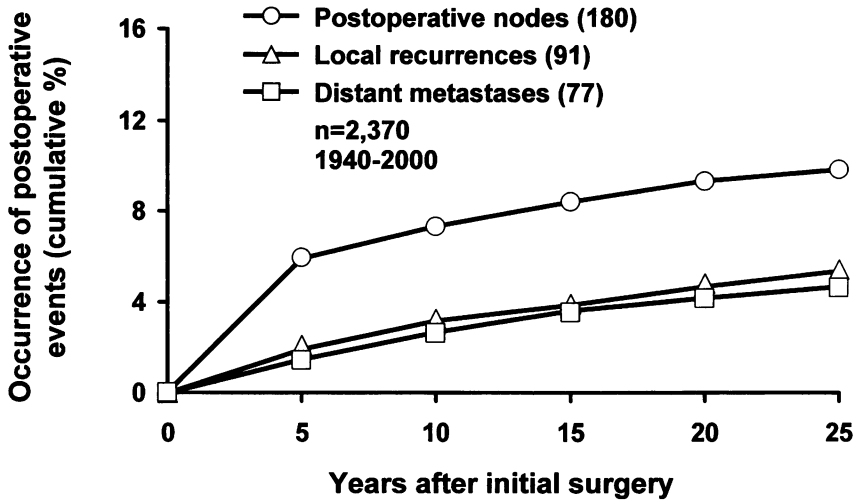

FIG. 6. Cumulative occurrence during 25 years of postoperative events: metastatic nodes (180 patients), local recurrences (91 patients), or distant metastases (77 patients). Data are based on 2,370 PTC patients with disease confined to the neck, who had initial complete tumor resection at Mayo Clinic during 1940 through 2000.

that the most frequent site of TR was in regional (neck) lymph nodes, accounting, to date, for 71% of the total number of first postoperative recurrent events. As illustrated in Figure 6, the 25-year recurrence

rates at regional, local, and distant sites were 9.8%, 5.5%, and 4.6%. At 40 postoperative years the comparable figures were 10%, 6% and 5%, respectively.

MACIS prognostic scores were <6 in 2,099 (83.6%), 6–6.6.99 in 215 (8.6%), 7–7.99 in 84 (3.3%) and 8+ in 114 (4.5%). The 25-year CSM rates for patients with scores of <6, 6–6.99, 7–7.99, and 8+ were 0.9%, 15%, 44%, and 63%, respectively ($P < 0.001$). The comparable 40-year CSM rates were minimally higher for those with scores of < 6 and 6–6.99 at 2.3% and 19%, respectively. However, there were no deaths from PTC between 20 and 40 postoperative years in those 198 patients who had scores of 7 or greater. Figure 7 illustrates survival to death from PTC, according to the MACIS low-risk (scores < 6) and high-risk (scores 6+) prognostic scheme, for the complete group of 2,512 patients ($P < 0.001$). At 25 postoperative years, the cause-specific survival rate for the 2,099 low-risk patients (with MACIS scores < 6) was 99.1%, and by 40 years the rate was 97.7%. Comparable cause-specific survival rates for the 413 high-risk patients (with MACIS scores of 6+) were at 25 years 65.4%, and at 40 years 63.0%.

Mortality and Recurrence Rates During 1940–1954 and 1955–2000

The CSM rate at 20 postoperative years was significantly higher ($P = 0.0001$) for the 338 patients treated during 1940–54, when compared to the rates seen for the 2,174 patients treated during 1955

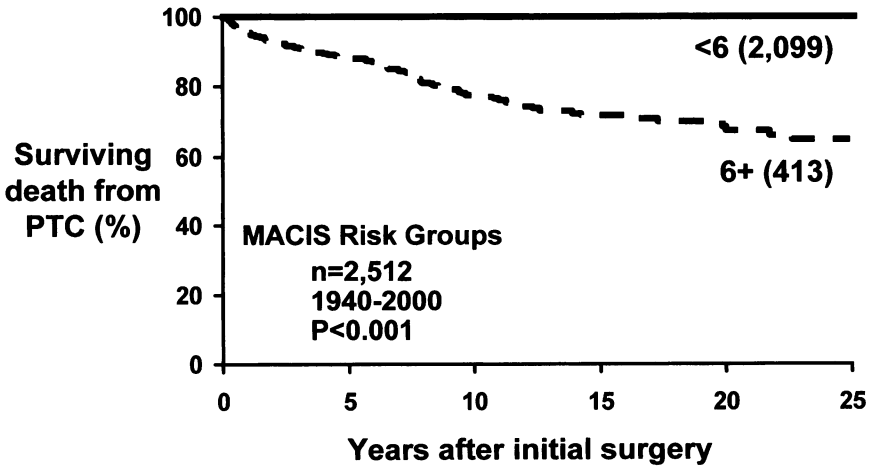

FIG. 7. Survival to death from PTC during 25 postoperative years in 2,512 patients managed during 1940 through 2000, according to MACIS low-risk (scores < 6) and MACIS high-risk (scores 6+) prognostic groupings. Numbers in parentheses represent the numbers of patients in each risk-group at the time of initial surgery.

through 2000 (Figure 8, left panel). At 15 postoperative years the CSM rate for the 1940–54 cohort was 7.4%, as compared to the rates of 4.9%, 4.0%, and 2.7% seen in the subsequent three eras ($P = 0.006$). At 40 postoperative years the CSM rate for the 1940–54 cohort was 12%, as compared to 5% in those treated during 1955–2000 ($P = 0.002$). There was no significant improvement in CSM rates during the three later eras of 1955–69, 1970–84, and 1985–2000 ($P = 0.14$). Similarly significant differences ($P < 0.001$) were seen for TR between the 1940–54 and the 1955–2000 cohorts of treated patients (Figure 8, right panel). At 15 postoperative years the TR rate for the 1940–54 cohort was 18.4%, as compared to the rates of 7.6%, 11.0%, and 11.7%, seen in the three later eras ($P < 0.0001$). At 40 postoperative years the TR rate for the 1940–54 cohort was 26%, as compared to 12% in the 1955–2000 cohort ($P < 0.001$).

Influence of Initial Unilateral Lobectomy on Mortality and Recurrence

As described in the preceding section, of the four eras studied, the CSM and TR rates were highest for the 338 patients initially treated during the 1940–54 era. During that 15 year period, 176 (52%) of the PTC patients underwent an initial unilateral lobectomy (UL), while 144 (43%) underwent bilateral lobar resection (BLR), comprising bilateral subtotal, near-total, and total thyroidectomy in 15%, 24%, and 4%, respectively. Figure 9 compares the cumulative occurrence rates

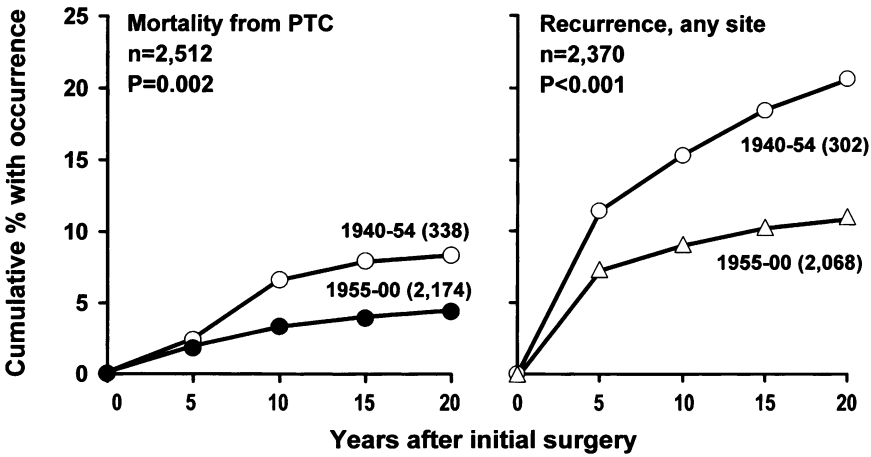

FIG. 8. Comparison of cumulative occurrence rates for CSM (left panel) and TR (right panel) between PTC patients treated during 1940–54 and those treated during 1955 through 2000.

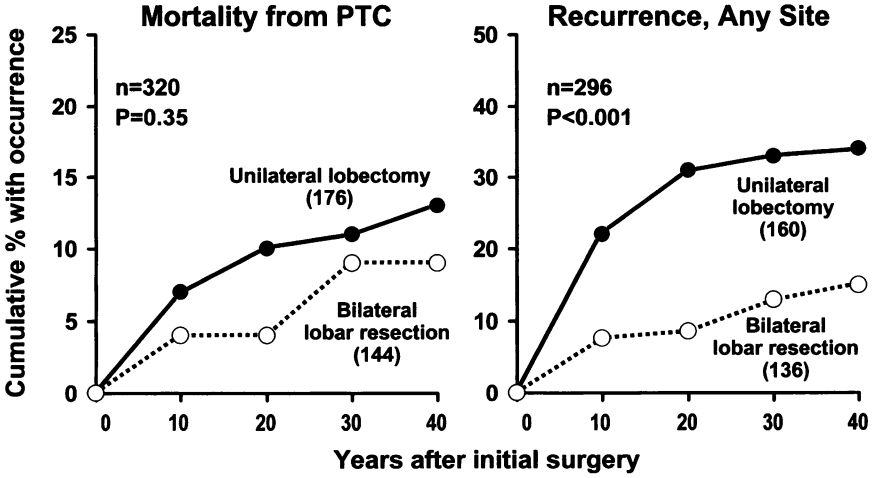

FIG. 9. Comparison of cumulative occurrence rates for CSM (left panel) and TR (right panel) between patients treated during 1940–54 by either unilateral lobectomy or bilateral lobar resection.

for CSM (left panel) and TR (right panel) between patients treated during 1940–54 by either UL or BLR. At 20 postoperative years CSM after UL was 10%, as compared to 4% after BLR. At 40 postoperative years the comparable figures were 13% and 9%. At 20 years the TR rates were 31% after UL and 9% after BLR. By 40 years the comparable TR rates were 34% and 15%. For the 1940–54 group of patients, the CSM difference failed to achieve statistical significance ($P = 0.31$). However, the TR rates after UL were very significantly higher than after BLR ($P = 0.0007$).

Figure 10 compares the outcome after either UL or BLR in MACIS scores < 6 (low-risk) patients treated during 1940–54 (upper panels) and MACIS 6+ (high-risk) patients (lower panels) treated during 1940 through 2000. There was no significant improvement in CSM rates in MACIS < 6 (low-risk) cases when patients were submitted to BLR, rather than UL ($P = 0.31$). The 20-year CSM rates after UL and BLR were 1.5% and 0.9%, respectively. By contrast, at 20 postoperative years there was an almost four-fold increase in TR after UL, as compared to BLR. The 20-year rate after UL was 26%, as compared to 7% after BLR. This difference in TR rates was highly significant ($P = 0.0007$). As shown in the lower panels of Figure 10, for high-risk patients (MACIS scores 6+) treated during 1940 through 2000, UL was associated with significantly higher rates for both CSM and TR. At 25 years the CSM rates after UL and BLR were 55% and 28% ($P =$

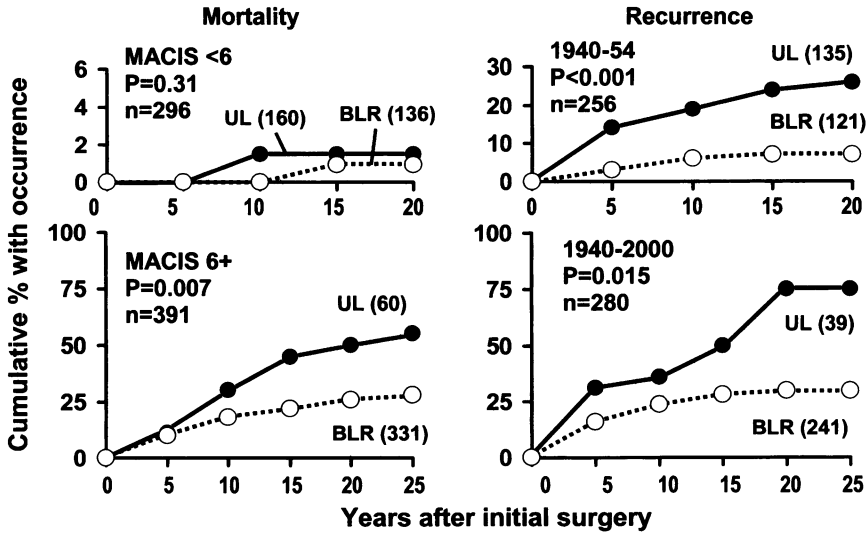

FIG. 10. Comparison of outcome after either unilateral lobectomy (UL) or bilateral lobar resection (BLR) in MACIS < 6 (low-risk) patients treated during 1940–54 (upper panels) and MACIS 6+ (high-risk) patients (lower panels) treated during 1940 through 2000. The left panels illustrate CSM in MACIS scores < 6 (upper) and 6+ patients (lower). The right panels show comparable rates for TR at any site for each of the two risk-groups.

0.007). The comparable rates for TR were 75% after UL and 30% after BLR ($P = 0.015$).

Outcome in Low- and High-Risk PTC during 1955–2000

Because of the significantly worse outcome seen for both CSM and TR in the 1940–54 era, further analysis of outcome was confined to the 1955–2000 cohort of 2,174 patients, of whom 1,835 (84%) had MACIS scores of less than 6. Figure 11 illustrates the trends during 1955 through 2000 in 10-year rates for CSM in both low-risk (MACIS < 6) and high-risk (MACIS 6+) patients. Although 10-year CSM rates in low-risk patients fell during the period studied from 1.1% to 0%, this difference was not statistically significant ($P = 0.24$). Similarly, a drop in 10-year CSM rates from 26% to 14% in high-risk patients failed to reach significance ($P = 0.13$). Figure 12 demonstrates the comparable trends during 1955 through 2000 in 10-year TR rates for both low-risk and high-risk patients. There was an insignificant minor decline in TR rates observed during the last era (1985–2000) in the high-risk cases. Curiously, the observed TR rates for the low-risk cases progressively rose from 5% in 1955–69, through 7.5% in 1970–84, to a figure of 8.3%

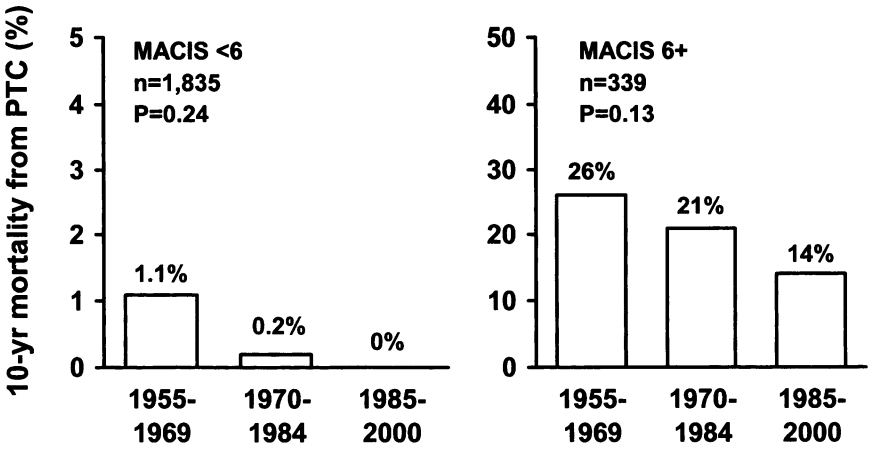

FIG. 11. Trends during 1955 through 2000 in 10-year rates for cause-specific mortality in (left panel) 1,835 PTC patients with MACIS scores < 6, and (right panel) in 339 patients with MACIS scores of 6+.

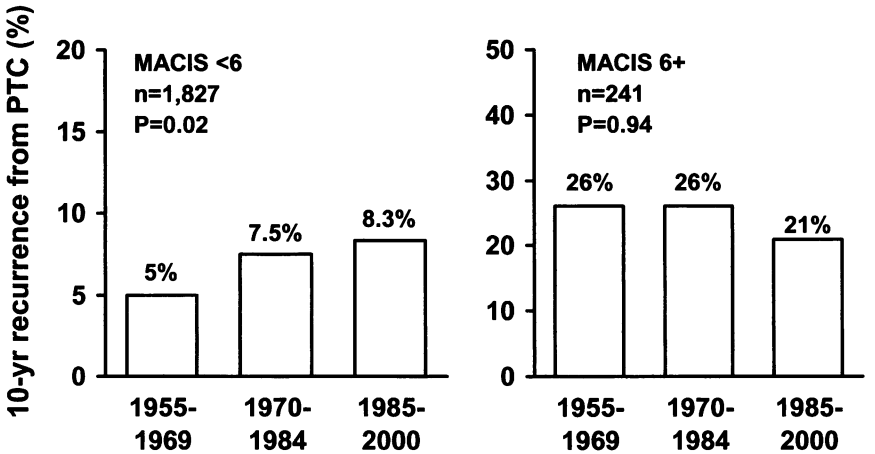

FIG. 12. Trends during 1955 through 2000 in 10-yr rates for tumor recurrence, any site, in (left panel) 1,827 PTC patients with MACIS scores < 6 and (right panel) in 241 patients with MACIS scores of 6+.

in 1985–2000, a trend that was statistically significant ($P = 0.02$). This upward trend in TR rates during the past 30 years may well reflect the increasing sensitivity of locoregional recurrence detection using immunometric assays of serum thyroglobulin (Tg) and, especially since 1985, the more frequent use of FNA biopsies guided by high-resolution ultrasound examination of the postoperative neck (27). Overall, despite the increasing use of RRA since 1970, there was no statistically

significant progressive improvement in outcome (as evidenced by both CSM and TR) in either the 339 high-risk or the 1,835 low-risk PTC cases treated at the Mayo Clinic during 1955 through 2000.

Lack of Influence of RRA on Outcome after Adequate Initial Surgery

In an attempt to quantify the influence of RRA on outcome after adequate initial surgery, the final analyses were performed only on the 1,163 MACIS low-risk (scores < 6) patients, who had undergone either near-total or total thyroidectomy during 1970 through 2000 for tumors confined to the neck and completely excised at initial neck exploration. All of these 1,163 patients were operated in a standard manner during these three decades by a small group of specialized Mayo staff surgeons, who had recognized expertise in endocrine surgery. The preoperative investigations and the postoperative care were provided by Mayo staff endocrinologists, who also prescribed and monitored the patients' postoperative thyroid hormone suppressive therapy.

During 1970 through 2000, 875 patients underwent initial near-total thyroidectomy (NT), while 502 had total thyroidectomy (TT). Of these, 848 (97%) of the NT group and 472 (94%) of the TT group had no distant spread at presentation and had complete tumor excision at initial surgery. Of these 1,320 patients in the potentially curable NT/TT group, 1,163 (88%) were at presentation classified as having MACIS scores of < 6. 498 (43%) of these low-risk patients had RRA within 6 months of the initial surgery. Those who received RRA were more likely to have had positive neck nodes at presentation ($P < 0.001$). Of 636 node-negative patients, 195 (31%) received RRA. However, of 527 node-positive patients, 303 (57%) were ablated.

Table 1 illustrates the lack of influence of RRA on outcome in 1,163 MACIS < 6 low-risk patients treated during 1970 through 2000 by initial NT or TT. 665 (57%) of the 1,163 patients constituted the NT/TT alone group, while 498 (43%) had NT/TT and RRA within 6 postoperative months. At 20 postoperative years the CSM rate for the surgery alone patients was 0.4% and, for the NT/TT and RRA group, it was insignificantly different at 0.6% ($P = 0.64$). At 20 years the TR rate was actually significantly higher in the ablated group (13% versus 8%: $P = 0.008$), likely reflecting the tendency to more readily ablate node-positive patients. When the patients were divided into node-negative and node-positive groups, there were no statistically significant differences in outcome (CSM and TR) between those having surgery alone and those who also received postoperative RRA. Interestingly, there were no deaths from PTC in the 636 node-negative cases and only 2 in the node-positive group. For the node-negative patients, the 20-year

TABLE 1
Lack of Influence of RRA on Outcome in 1,163 MACIS Low-risk (Scores < 6) Patients Treated During 1970 Through 2000 by Near-Total (NT) or Total Thyroidectomy (TT)

Low-Risk (MACIS <6) 1970-2000	20-yr Mortality NT/TT Alone	20-yr Mortality NT/TT and RRA	20-yr Recurrence NT/TT Alone	20-yr Recurrence NT/TT and RRA
All patients (n=1,163)	0.4%	0.6% (P=0.64)	8.3%	12.7% (P=0.008)
Node-negative (n=636)	0%	0% (P=NA)	3.4%	4.3% (P=0.80)
Node-positive (n=527)	1.2%	0.9% (P=0.99)	19.5%	19.9% (P=0.19)

TR rates were 3.4% after surgery alone, and 4.3% after surgery and RRA ($P = 0.80$). For the node-positive group, who clearly had much higher TR rates, the CSM rates at 20 years were 1.2% after surgery alone and 0.9% after RRA ($P = 0.99$). The 20-year TR rates only differed by 0.4%, being 19.5% for surgery alone and 19.9% for surgery and RRA ($P = 0.19$).

DISCUSSION

The present study carefully chronicles the changes in initial management of 2,512 consecutive patients with the commonest endocrine malignancy, PTC, treated at the Mayo Clinic in Rochester, Minnesota, during 1940 through 2000. During that 61-year period there were two significant therapeutic trends. The first of these was a change in surgical practice during 1940–69 from an initial unilateral (total) lobectomy (UL) to a bilateral lobar resection (BLR). This resulted in significantly improved TR rates in both low-risk and high-risk patients, and also reduced CSM rates in high-risk patients, as defined by the MACIS prognostic scoring system. These results were consistent

with our previously reported studies, published in 1987 (28) and 1988 (29), on patients classified by the AGES prognostic scoring system and treated at Mayo during 1946 through 1970. They also lend further support to our more recent results published in 1998, which were derived from studies of outcome in 1,685 AMES low-risk PTC patients treated at Mayo during 1940 through 1991 (6). In this latter study, there were no differences in the rate of developing distant metastases between UL and BLR, but after UL 20-year rates for local recurrences and neck nodal metastases were 14% and 19%, significantly higher than the 2% and 6% seen after BLR ($P = 0.0001$). From these studies it may be concluded that UL, although not associated with higher CSM rates in low-risk cases, has certainly been associated with a significantly higher risk of locoregional recurrence. Thus, as practiced at Mayo since 1955, BLR probably does represent the preferred initial surgical approach in all patients with PTC, even in those 80–85% of PTC patients classified as being at low-risk of CSM, whether by AGES (28), AMES (6), or MACIS (26) prognostic systems.

The second significant change in initial therapy seen in this study occurred around 1976, and again in 1980. During these times, as illustrated in Figure 4, the frequency of RRA after BLR increased abruptly by 23% and 29%, respectively. It is probably no coincidence that these two remarkable shifts in policy occurred exactly at the same times that Dr. Mazzaferri presented to national societies, such as the Society for Nuclear Medicine and the American Thyroid Association, his 6-year (30) and 10-year (31) follow-up reports on the impact of therapy in 576 PTC patients registered with the US Air Force Central Tumor Registry. In these two initial reports (30,31), he described the successful outcome of 33 patients who received I-131 postoperatively to ablate macroscopically normal thyroid tissue in post-surgical remnants. By 1997, Mazzaferri (32) had extended his USAF and Ohio State cohort to include 151 patients with differentiated thyroid cancer (DTC) undergoing RRA and followed for a mean of 15 years. From the outcome results in these patients, he enthusiastically concluded that "thyroid remnant ablation is effective in reducing recurrence of DTC in patients of all ages and reduces the risk of death from thyroid carcinoma in patients > age 40 at the time of diagnosis". Such a bold conclusion would not be justified from our present study where, despite increased use of RRA, there was no statistically significant progressive improvement in outcome, as measured by CSM or TR rates, in either the 339 high-risk (MACIS scores 6+) or the 1,835 low-risk (MACIS scores < 6) PTC cases managed at the Mayo Clinic during 1955 through 2000.

As has been emphasized in an elegantly crafted paper by our former colleague, Dr. Gorman (33), "numerous studies support the use of radioiodine in the treatment of metastatic disease; but extrapolation to the practice of remnant ablation does not follow". After he demonstrated that in DTC ablative therapy directed to post-surgical remnants "reduced visible I-131 uptake to zero or nearly zero, but did not protect against tumor recurrence", Dr. Gorman described the practice of RRA as the "questionable pursuit of an ill-defined goal". In an accompanying editorial to this paper, Dr. Sisson from Ann Arbor (34) observed that "scintigrams have come to be worshiped as portents and as arbiters of proper treatment". From a review of the then available literature, which he described as "a statistical labyrinth", he concluded (34) that "the aggregate of evidence does not convincingly demonstrate that ablation of small remnants—and especially those remote from the primary tumor—lowers the rate of recurrent cancer. Bearing these concepts in mind, each physician must decide from incomplete knowledge whether to use I-131 as a radioactive eraser".

In pursuing this present long-term study, which was commenced just after the publication of the papers of Gorman (33) and Sisson (34) in 1983, an over-riding desire has been to determine whether the aggressive postoperative use of RRA is justifiable, or whether a more selective use of I-131 in this context is a more reasonable approach. As has been described in this paper's present results, the more widespread use of RRA has not been associated with a significant improvement in the already excellent CSM and TR rates found in PTC patients with MACIS scores < 6. In such low-risk PTC patients, an initial management program, consisting of BLR (usually near-total thyroidectomy), conservative neck nodal excision, and modest postoperative levothyroxine suppressive therapy, would appear to be justified.

In a 1994 editorial, in the American Journal of Medicine, Dr. DeGroot (35) summarized the status of RRA as follows: "Mazzaferri, Young and coworkers provided, nearly two decades ago, the first powerful support for the role of radioiodine treatment in reducing recurrences and deaths in differentiated (thyroid) cancer... more recent studies by DeGroot and colleagues, and Samaan and coworkers demonstrated, in a careful analysis, stratifying patients by extent of disease, that both more extensive surgery (lobectomy plus subtotal or near-total thyroidectomy) and radioactive iodine treatment reduce the number of recurrences and deaths. Hay and coworkers have thrown their support behind more extensive surgery, but have not yet supported routine radioactive iodide ablation".

It is still our stance that routine RRA in all PTC patients is unjustifiable, and, in our opinion, the outcome results, described in this report, should raise very serious doubts about the efficacy of RRA in eliminating tumor recurrence in patients with low-risk (MACIS < 6) PTC. For that reason the Division of Endocrinology at Mayo Clinic, Rochester, has, since 1994, stopped recommending RRA to patients with low-risk (MACIS < 6) PTC. On the other hand, RRA is still being advised for the postoperative management of those few patients who are, (with initial MACIS scores of 6+), at significantly increased risk of both tumor recurrence and death from papillary cancer.

In our opinion, we are moving much closer to providing satisfactory answers to Sisson (34), who in 1983 suggested that, in the treatment of PTC, "to ablate or not to ablate is a question that will haunt us for some time to come". It is our wish that, for patients with low-risk (MACIS < 6) PTC, the era of the "radioactive eraser" will soon be a memory from the last quarter of the twentieth century. We sincerely hope that these results may serve as the death knell for the use of Iodine-131 for remnant ablation in low-risk PTC patients who have had adequate initial surgery, with complete tumor excision. It should be emphasized that patients with typical PTC have a very high chance of 'cure' after surgery and levothyroxine therapy: a 25-year cause-specific survival rate of 100% for 636 node-negative MACIS < 6 PTC patients cannot be improved by remnant ablation.

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DISCUSSION

Carey, Charlottesville: I enjoyed that presentation very much. In your retrospective study, did you have a chance to look at TSH suppression as an independent variable?

Hay, Rochester: I think, as you would appreciate, that the problem in many previously published human thyroid cancer studies has been the variation in primary therapy preceding the introduction of postoperative TSH suppression. I think, if we identified from our current study all ablated patients, who had a prior near-total or total thyroidectomy, and within that group we compared outcome results in those who had a modest degree of TSH suppression with those who had absolute extinction of TSH, we may be able to provide you with some preliminary answers to your question. However, to date, neither we, nor to my knowledge, have any other workers in this area done such controlled studies. At our institution, since about 1994, our clinical practice has been to employ only a modest degree of TSH suppression (typically 0.1 to 0.4 mU/l) in the majority of papillary cancer patients, who are at low-risk of tumor recurrence, and to restrict true TSH suppression (serum levels <0.1 mU/l) to that minority of PTC patients, who are at high-risk of cause-specific mortality. But, at this time, I do not think that there exists any good published scientific data to provide a sound basis for such a practice.